UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,003	03/22/2001	David M. Sabatini	WIBL-P02-001	5682

21559 7590 07/12/2006

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,003	SABATINI, DAVID M.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *160-177 and 237-240* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *160-177 and 237-240* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 4/24/06 has been acknowledged.
Claims 160-177 and 237-240 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **571-273-8300.**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/24/06 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 160-177 and 237-240 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an array of transfected cells having density of 330 locations per square centimeter, does not reasonably provide enablement for an array of transfected eukaryotic cells that have density more than 330 locations per square centimeter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of invention as claimed encompasses an array of transfected cells having a density of location ranging from 96 to 1,000, 000 locations per square centimeter. At best the specification teaches preparation of transfected cell micro array using PixSys 5500 Robotic Arrayer with Telechem's Arraylt Stealth Pins (SMP4) which is capable providing a location of 150um diameter wherein each spotted location is 400 um apart (spec example-3, fig-4). Therefore given the geometric constrains the specification is only enabled to make an array of transfected cells, which comprises only 330 locations per square centimeter [$1x10^8/(150+400)^2$]. The USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of skill. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). Furthermore, It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but*

compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In instant case making transfected cell micro array is not considered routine in the art and without sufficient guidance regarding how to make the claimed location density and use thereof the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claim Rejections - 35 USC § 102

Claims 160-175 and 237-240 are rejected under 35 U.S.C. 102(e) as being anticipated by Hozier (US 5,563,060, 1996).

The scope of instant claims encompasses an array of transfected eukaryotic cells comprising a surface having an array of at least 96 locations having density of 100 locations per square centimeter, wherein each location comprises eukaryotic cells that are transfected with one or more defined nucleic acid molecules.

Hozier teaches micro libraries for screening cell population. The cited art teaches that micro library comprises microscopic subpopulations immobilized on a surface wherein each subpopulation is formed from between 1 to 1,000,000 cells and the approximate density of said sub-populations is between 10 sub-populations per mm square and $10x10^6$ sub-populations per mm square (col.23, lines 57-67, col.24, lines

60-67). The cited art further teaches that micro library contains cells containing exogenous DNA (col.24, lines 14-18, col.15, lines 24-34). The cited art further teaches micro libraries comprising human genomic or cDNA libraries (col. 25, lines 1-15). The cited art further teaches that micro-libraries comprise variety of cells that include any eukaryotic cell (col. 24, lines 27-35). The cited art further teaches preparation of predetermined arrays (col.11, lines 58-67). Thus the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

Claim 176 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hozier (US 5,563,060, 1996) as applied to claims 1160-175 and 237-240 above, and further in view of Montgomery et al (Proc Natl Acad Sci U S A. 95(26): 15502-7, 1998).

Hozier is relied upon as described in rejection above. However, Hozier does not teach the use double-stranded RNA molecule or nucleic acid molecule having a modified base or backbone.

Montgomery teaches the double-stranded RNA mediated genetic interference in C.elegans. Regarding claim 176 the cited art teaches a nucleic acid molecule, which encodes double-stranded RNA for RNAi experiments (page 15502, col2. para.2). Regarding claim 177 the cited art teaches gene-specific probes for insitu hybridization, wherein the probe comprises Digoxigenin (DIG)-labeled single stranded DNA probe (page 15503, col.2, para. 3).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Hozier by substituting the nucleic acid molecules with a double-stranded RNA molecule or a nucleic acid molecule having a modified base or backbone. One would have been motivated to incorporate a double-stranded RNA molecule to inhibit the expression of a gene of interest. One would have been motivated to use a nucleic acid molecule as probe to analyze the gene expression of interest. One

would have reasonable expectation of success, since transduction of eukaryotic cells with nucleic acid molecules has been routine in the art at the time of filing. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Claims 160-168, 171-174 and 240 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Taylor et al (US 6,103,479 2000).

The scope of instant claims encompasses an array of transfected eukaryotic cells comprising a surface having an array of at least 96 locations having density of 100 locations per square centimeter, wherein each location comprises eukaryotic cells that are transfected with one or more defined nucleic acid molecules.

Taylor teaches making of miniaturizes high-throughput cell array and an apparatus for cell-based screening. Regarding claim 160 the cited art teaches spots of eukaryotic cells spotted at the resolution of 200 um or 400 um spot patterns, which is capable of inherently providing spot density of at least 2500 or 625 locations per square centimeter respectively at such a resolution (see figure 3B, col. 7, lines 21-24), which is well with the density of locations claimed in the instant application (i.e. 100-1000 locations per square centimeter. In addition the cited art further discloses miniaturizes high-throughput cell array, which comprises at least 96 locations (see figure 18A-B, col. 8, lines 10-14, col.20, lines 10-15). The cited art teaches that a cell micro array comprises the dimensions of 20mmX30mm (col.16, lines 45-50). The cited art further teaches that each a cell based assay that requires area equivalent to a well size of 0.2 to 1.0mm diameter (col.6, lines 11-19). Accordingly the cited art clearly anticipates an array of at least 100-500 locations having density in the range of 100 locations per square centimeter.

The cited art further teaches that the preferred cell types for the micro-patterned array include lymphocytes, cancer cells, fibroblasts, neurons, fungi, bacteria and other prokaryotic and eukaryotic cells (col.13 lines 5-35). The cited art further teaches micro-patterns at discrete locations comprises array of different forms, which accommodate a

sample size from 1 nanoliter (nl) to 1000nl (col.9 lines 7-10). The cited art further teaches that the size of a well on micro-patterned array ranges from 200 μm to 400μm, which would inherently provides providing spot density of at least 2500 or 625 locations per square centimeter (see figure 3B, col. 7, lines 21-24). Regarding claims 161-164 and 166 the cited art teaches that the cells attaches to the wells can be modified with luminescent of cell chemical or molecular properties. The indicators can be introduced into the cells before or after the cells were seeded onto array by any one or combination of variety of physical methods such as diffusion across the cell membrane, mechanical perturbation of cell membrane or genetic engineering so that they express under prescribed conditions. The cited art further teaches the use of reporter genes which encodes chemiluminescent proteins, which permits the analysis of the physiological state of cells when contacted with drugs or other reactive substances (Col.12 lines 44-67, col. 13, line 1-4, col.13, lines 29-30). Regarding claim 165 the cited art teaches that the cells suspended in culture media at concentration from about 10^3-10^7 cells per ml are incubated in contact with the wells. The cited art teaches that the density of cells attached to wells is controlled by the cell density in the cell suspension, time permitted for cell attachment to the well surface (col.12, lines 13-36). Thus given the broadest reasonable interpretation the cited art clearly teaches an array of transfected eukaryotic cells as claimed.

Response to Arguments

Applicant's arguments filed on pages 2-5 dated 04/24/06 regarding prior art issues have been fully considered but they are not persuasive. The applicant argues that Taylor does not describes an array of lat least 96 locations of transfected cells having a density of 100 locations per square centimeter. However, applicant's arguments are found not persuasive for the same reasons of record as set forth above because the cited art clearly teaches: i) spots of eukaryotic cells spotted at the resolution of 200 um or 400 um spot patterns, which is capable of inherently providing spot density of at least 2500 or 625 locations per square centimeter respectively at such a resolution (see figure 3B, col. 7, lines 21-24), which is well with the density of locations claimed in the instant application (i.e. 100-1000 locations per square centimeter.ii) miniaturizes high-

throughput cell array, which comprises at least 96 locations (see figure 18A-B, col. 8, lines 10-14, col.20, lines 10-15) and a cell micro array comprises the dimensions of 20mmX30mm (col.16, lines 45-50). iii) a cell based assay that requires area equivalent to a well size of 0.2 to 1.0mm diameter (col.6, lines 11-19), which at this resolution is cable of providing at least 100-500 locations having density well within the range of 100 locations per square centimeter as claimed in the instant application. Thus given the broadest reasonable interpretation the invention as claimed obvious over the cited art of record if not anticipated.

Claim 176 is rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al (US 6103,479 2000) as applied to claims 160-168, 171-174 and 240 above, and further in view of Montgomery et al (Proc Natl Acad Sci U S A. 95(26): 15502-7, 1998).

Taylor et al is relied upon as described in rejection above. However, Taylor does not teach the use double-stranded RNA molecule or nucleic acid molecule having a modified base or backbone.

Montgomery teaches the double-stranded RNA mediated genetic interference in C.elegans. Regarding claim 176 the cited art teaches a nucleic acid molecule, which encodes double-stranded RNA for RNAi experiments (page 15502, col2. para.2). Regarding claim 177 the cited art teaches gene-specific probes for insitu hybridization, wherein the probe comprises Digoxigenin (DIG)-labeled single stranded DNA probe (page 15503, col.2, para. 3).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Taylor by substituting the nucleic acid molecules with a double-stranded RNA molecule or a nucleic acid molecule having a modified base or backbone. One would have been motivated to incorporate a double-stranded RNA molecule to inhibit the expression of a gene of interest. One would have been motivated to use a nucleic acid molecule as probe to analyze the gene expression of interest. One would have reasonable expectation of success, since transduction of eukaryotic cells

with nucleic acid molecules has been routine in the art at the time of filing. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Response to Arguments

Applicant's arguments filed on pages 5-7 dated 04/24/06 regarding prior art issues have been fully considered but they are not persuasive. The applicant argues that Taylor does not describe an array of at least 96 locations of transfected eukaryotic cells having a density of at least 100 locations per square centimeter and Montgomery does not remedy this deficiency. However, applicant's arguments are found not persuasive for the same reasons of record as set forth above because the cited art clearly teaches: i) spots of eukaryotic cells spotted at the resolution of 200 um or 400 um spot patterns, which is capable of inherently providing spot density of at least 2500 or 625 locations per square centimeter respectively at such a resolution (see figure 3B, col. 7, lines 21-24), which is well with the density of locations claimed in the instant application (i.e. 100-1000 locations per square centimeter, ii) miniaturizes high-throughput cell array, which comprises at least 96 locations (see figure 18A-B, col. 8, lines 10-14, col.20, lines 10-15) and a cell micro array comprises the dimensions of 20mmX30mm (col.16, lines 45-50), iii) a cell based assay that requires area equivalent to a well size of 0.2 to 1.0mm diameter (col.6, lines 11-19), which at this resolution is cable of providing at least 100-500 locations having density well within the range of 100 locations per square centimeter as claimed in the instant application.

The applicant argues that even if Taylor described an array having the required parameters, instant claim would still not be obvious over Taylor in view of Montgomery, because the cited references provide no motivation for one to replace the reporter gene employed by Taylor with any other nucleic acid molecule. The applicant argues that Taylor of Montgomery does not provide any motivation to replace the reporter gene with nucleic acid encoding double stranded RNA.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Taylor clearly teaches the use miniaturized cell array for drug screening for potential interaction of variety of substances like DNA and RNA (col.2, lines 7-50). The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law (See MPEP 2144). One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus the invention as claimed is *prima facie* obvious in view combined teaching of cited prior art of record.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER